



Behavioural sleep problems in children with attention deficit/hyperactivity disorder (ADHD): Protocol for a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004070
Article Type:	Protocol
Date Submitted by the Author:	19-Sep-2013
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Mental health
Keywords:	attention deficit disorder with hyperactivity, sleep, comorbidity

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**Behavioural sleep problems in children with attention deficit/hyperactivity disorder (ADHD):
Protocol for a prospective cohort study.**

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Running title Behavioural sleep problems in children with ADHD

Date 18 September 2013

Word count 2995 (Abstract 294)

Key words attention deficit disorder with hyperactivity, sleep, child, comorbidity, mental
health

Abbreviations

ADHD Attention-deficit/hyperactivity disorder

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition

OSA Obstructive sleep apnoea

ADIS-C Anxiety Disorders Interview Schedule for Children/Parent version, fourth edition

RCT Randomised controlled trial

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they, their spouses, partners or children do not have any financial and non-financial relationships with companies that may be relevant to the submitted work to declare.

Author contribution

KL, HH, ES and FM conceived the study. KL coordinated the study and drafted the current manuscript, supervised by HH, ES and FM. AG participated in the coordination of the study and drafted the current manuscript, supervised by KL. All authors contributed, read and approved the final manuscript.

ABSTRACT

Background: Children with ADHD commonly experience behavioural sleep problems, yet these difficulties are not routinely assessed and managed in this group. Presenting with similar symptoms to ADHD itself, sleep problems are complex in children with ADHD and their aetiology is likely to be multifactorial. Common internalising and externalising comorbidities have been associated with sleep problems in children with ADHD; however, this relationship is yet to be fully elucidated. Furthermore, limited longitudinal data exist on sleep problems in children with ADHD, thus their persistence and impact remain unknown.

Study aims: In a diverse sample of children with ADHD, this study aims to: 1) quantify the relationship between sleep problems and internalising and externalising comorbidities; 2) examine sleep problem trajectories; and 3) examine the impact of sleep problems on children and their families over a 12-month period.

Methods and analysis: Prospective cohort study of 400 children with ADHD (150 with no/mild sleep problems, 250 with moderate/severe sleep problems) recruited from paediatric practices across Victoria, Australia. The children’s parents and teacher provide data at baseline and 6- and 12-months post enrolment. *Key measures:* parent-report of child’s sleep problem severity (no, mild, moderate, severe); specific sleep domain scores assessed using the Child Sleep Habits Questionnaire; internalising and externalising comorbidities assessed by the Anxiety Disorders Interview Schedule for Children IV/Parent version. *Analyses:* Multiple variable logistic and linear regression models examining the associations between key measures, adjusted for confounders identified *a priori*.

Ethics and dissemination: Ethics approval has been granted. Findings will contribute to our understanding of behavioural sleep problems in children with ADHD. Clinically, they could improve the assessment and management of sleep problems in this group. We will seek to

publish in leading paediatric journals, present at conferences and inform Australian paediatricians through the *Australian Paediatric Research Network*.

For peer review only

ARTICLE SUMMARY

Article focus

- Behavioural sleep problems are common in children with ADHD as are internalising and externalising comorbidities; both of which are associated with poorer child and family well-being.
- However the relationship between sleep problems and internalising and externalising comorbidities is yet to be quantified. Doing so may prompt clinicians to better address sleep problems, which do not appear to be routinely assessed and managed in the care of children with ADHD.
- Almost all studies investigating sleep problems in children with ADHD are cross-sectional and thus the trajectories of sleep problems and their relative impact on child and family well-being are unclear.

Key messages

- Elucidating the relationship between sleep problems and internalising and externalising comorbidities could inform their clinical assessment and management.
- This study will provide the first longitudinal data on the trajectories of sleep problems that are generalisable to the wider population of children with ADHD.
- This study will quantify the relative impact of sleep problems on child and family well-being over time, thereby informing clinicians and families of the relative importance of managing sleep problems in children with ADHD.

Strengths and limitations of the study

- The sample is recruited from a geographically diverse population of children with ADHD and represents the case mix seen in clinical practice, thus improving generalisability of the findings.
- Limitations of this study include lack of direct assessments of child sleep and exclusion of non-English speaking families.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder that leads to impairment across multiple domains including social and academic functioning.¹ ADHD affects up to 5% of children worldwide² and is commonly accompanied by sleep problems.³ Between 55-74% of parents report sleep problems in their child with ADHD⁴⁻⁸ and these are typically behavioural in nature (ie, extrinsic cause) and can include difficulty falling asleep and bedtime resistance.⁶ Primary sleep disorders (ie, intrinsic cause) such as restless leg syndrome and sleep disordered breathing are also elevated in children with ADHD compared to typically developing children.^{9, 10 11} Yet, despite a long standing recognition of sleep problems prevalence,^{12, 13} and evidence that they are associated with poorer child and family well-being,⁶ sleep problems do not appear to be routinely assessed or managed by clinicians caring for children with ADHD.⁶

Identifying sleep problems in children with ADHD is challenging. Sleep deprivation closely mimics symptoms attributed to ADHD (eg, inattention, hyperactivity)^{9, 14} and objective and subjective measures of sleep often conclude disparate findings.¹⁴ Objective measures (eg, polysomnography, actigraphy) – the ‘gold standard’ – produce reliable findings for parameters such as sleep duration¹⁵ but feasibility and costs are often barriers to their use in large studies.¹⁶ In addition, they do not capture behavioural sleep problems such as bedtime resistance and limit setting disorders – which are more common in children with ADHD. On the other hand, subjective measures (eg, parent report) are a valid screening tool for behavioural sleep disorders¹⁵ yet can over-estimate sleep duration, under-estimate night-waking,^{15, 16} and can also be influenced by parent mental health.¹⁷ Thus parent report is ideal for large studies where behavioural sleep problems are the key focus. Furthermore, parent report reflects parental concern, which is a key driver for seeking health professional advice around sleep.¹⁸

The mechanisms associated with sleep problems in children with ADHD are complex and appear multi-factorial.⁹ Both sleep problems and ADHD are regulated by the central nervous system, thus there is a strong neurobiological overlap.^{3, 9, 19} Empirically, this is supported by the recognition that ADHD symptom severity worsens in the presence of sleep problems.^{6, 20, 21} Similarly, stimulant medications (eg, methylphenidate), which also work on the central nervous system, have been associated with sleep problems, in particular delayed sleep-onset latency.^{13, 20-22} Yet, many stimulant naïve children also experience sleep problems,⁵ therefore other factors have received increasing investigation. In typically developing children, sleep problems have been associated with internalising (eg, mood disorders, anxiety disorders) and externalising (oppositional defiant disorder, conduct disorder) comorbidities.²² Research suggests that this is also the case for children with ADHD.^{20, 21, 23-25} However, this relationship is yet to be fully elucidated. Previous studies are often limited to single clinical samples^{8, 20, 21, 26, 27} and exclude children with common comorbidities or those taking ADHD medication.^{23, 24, 28} Furthermore, researchers are yet to consider children with co-occurring internalising and externalising comorbidities. Elucidating the relationship between sleep problems and internalising and externalising comorbidities in children with ADHD is likely to inform clinical practice around the assessment and management of sleep problems in this group.

Clinical management of sleep problems is also restricted by the lack of longitudinal data, which would inform the prognosis and thus the relative importance of managing sleep problems in children with ADHD. Although behavioural sleep problems are common in typically developing children, they are often transient and likely to resolve naturally.²⁹ However, in children with major depression, sleep problems have been shown to persist even after successful treatment.³⁰ The nature and persistence of sleep problems in children with ADHD is unclear. In a longitudinal study of a clinical sample of children referred with

ADHD, anxiety, or both (n=76, age 7 to 13 years), sleep problems were more likely to persist in this group over an 18-month period compared with a control group of children without a history of accessing mental health services recruited from nearby schools (n=31).³¹ The generalisability of these findings is limited by the small sample size and mixed sample of children with anxiety and ADHD. Longitudinal studies that can be generalised to the wider population of children with ADHD are required to understand trajectories and prognosis of sleep problems in ADHD.

Furthermore, longitudinal data could assess the burden of sleep problems in ADHD. Cross-sectionally, children with ADHD and parent-reported sleep problems have higher ADHD symptom severity,^{20, 21, 32} poorer quality of life, daily functioning and school attendance; and their caregivers are also more likely to be miss work and have poorer mental health⁶ compared to children with ADHD without sleep problems. However, the cross-sectional nature of these studies makes it impossible to delineate the sequence of sleep problems and other difficulties with functioning. Identifying the long-term impact sleep problems have on the functioning of children with ADHD is important to rationalise time and financial investment in the identification and management of sleep problems by health professionals and families.

STUDY AIMS

Through establishing a diverse cohort of children with ADHD recruited from multiple clinical practices, our study aims to address some of the previous limitations identified. The primary aim of the study is to examine associations between sleep problems and internalising and externalising comorbidities, considering parent reported moderate/severe behavioural sleep problems (Aim 1a); and sleep problem domains (eg, bedtime resistance, sleep anxiety) (Aim 1b). Through longitudinal study of the cohort over a one year period we will examine

the trajectories of behavioural sleep problems and predictive risk factors (Aim 2); and examine longitudinal relationships between behavioural sleep problems and child and family well-being, specifically in the domains of child quality of life, school attendance, parent mental health, family functioning, and work attendance (Aim 3).

METHODS AND ANALYSIS

Our prospective cohort study of children with ADHD (see Figure 1) runs from April 2011 to July 2014, encompassing participant recruitment, baseline and follow-up data collection and data analysis. The study is approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (30033; 28017) and Victorian Department of Education and Early Childhood Development (000573; 001307).

Study procedure

Paediatric practice recruitment

Personalised emails are sent to paediatricians working in public and private practice inviting them to assist with participant recruitment. In Australia, many general paediatricians work in public and private practice and the most common condition they manage is ADHD.³³ We identified paediatricians through the *Australian Paediatric Research Network*³³ and our knowledge of paediatricians who treat children with ADHD in the state of Victoria. Paediatricians pre-identify children with ADHD who they have seen within the past 12 months. An ‘opt out’ letter, signed by the paediatrician, is sent to the child’s primary caregiver, asking them to contact the study team if they *do not* wish to be contacted about the study. If caregivers do not ‘opt out’ within a two-week period, paediatricians pass the family’s contact details onto the research team. This method has previously resulted in a good uptake rates.³⁴

Family recruitment

The research team telephone families to assess eligibility. Interested, eligible families are mailed a participant information statement, consent form and parent baseline questionnaire. Families are enrolled upon receipt of written informed consent and the baseline questionnaire. To determine the extent of participation bias, data collected will be compared with non-participants including child gender, child age, and socioeconomic status of the family's immediate neighbourhood.

Participants

Inclusion criteria

Eligible children are aged 5 to 13 years who have a previous ADHD diagnosis, are currently experiencing ADHD symptoms and whose care-giver can report on their sleep, as below.

ADHD: Children identified by their treating paediatrician will have a confirmed diagnosis of ADHD, which in accordance with national recommendations requires confirmation of cross-situational impairment at kinder or school as well as home.³⁵ ADHD symptoms must also be current and are therefore assessed during the recruitment call, using the validated 18-item ADHD Rating Scale (DSM-IV)³⁶ and study-designed questions assessing ADHD diagnosis as per DSM-IV.³⁷ The study designed questions include: (a) symptom duration ('*Did your child have these symptoms for six months or longer before he/she was diagnosed with ADHD?*'); (b) age of onset ('*Did your child have these symptoms before he/she turned seven?*'), and (c) cross-situational impairment ('*Are these symptoms present at home, school or when out socially (eg, in the park, visiting friends?)*').

Sleep problem is determined by parent report of their child's sleep; parents are asked "Has your child's sleep been a problem for you over the past 4 weeks?" If the parent responds 'yes', they are asked to rate the severity of the problem (mild/moderate/severe).^{6, 29, 38} In typically developing children, of those whose parents report a moderate/severe sleep problem, 90% fall in the clinical range on the validated Child Sleep Habits Questionnaire.³⁹ Furthermore, parent report of moderate/severe sleep problems is associated with poorer child learning by blinded teacher report²⁹ and poorer child and family well-being.⁶ During the recruitment call if parents report that their child has a moderate/severe sleep problem they are asked several questions to establish whether the sleep problem meets the *International Classification of Sleep Disorders* criteria for at least one behavioural sleep disorder⁴⁰ or corresponds with night-time anxiety. Children with a moderate/severe sleep problem that meets at least one of these criteria are eligible for the *Sleeping Sound with ADHD study*, a randomised controlled trial (RCT) investigating whether treating sleep problems in children with ADHD can reduce ADHD symptoms.⁴¹ Children with no/mild sleep problems are eligible for the *Attention to Sleep study*, an observational cohort study.

Exclusion criteria

Children are excluded at the recruitment call if parents report any of the following criteria:

- 1) receiving specialised help for their sleep from a psychologist or a specialised sleep clinic;
- 2) serious medical condition (eg, severe cerebral palsy) or an intellectual disability (IQ < 70);
- 3) suspected obstructive sleep apnoea (OSA). OSA is assessed using the three sleep disordered breathing items from the Children's Sleep Habits Questionnaire.⁴² Parents who report that their child 'sometimes or usually snores loudly', 'stops breathing' and/or 'snorts/gasps' during their sleep are contacted by a paediatrician (HH) for further assessment. If OSA is suspected, children are referred to appropriate services;

4) family does not speak sufficient English to complete recruitment call or questionnaires.

Data collection

Immediately post enrolment, families are sent a 7-day sleep and medication log to complete during a typical school week and scheduled for a phone interview to assess child internalising and externalising comorbidities (described below). If the primary caregiver consents, the child's teacher is also sent a brief survey to assess classroom behaviour. Teachers are not informed of the child's sleep problem severity or ADHD status. Follow-up surveys are sent to the child's primary caregiver and teacher at 6- and 12-months post enrolment (see Table 1).

Measures

Internalising and externalising comorbidities are assessed by the Anxiety Disorders Interview Schedule for Children/Parent version IV (ADIS-C).⁴³ The ADIS-C is a semi-structured interview that allows, "for research purposes, reliable and valid diagnosis" according to DSM-IV criteria."⁴⁴ The ADIS-C is validated for administration over the telephone with parents - an important practical consideration - and yields excellent to acceptable 7-to-14-day test-retest reliability estimates for parents ($k=.65-1.00$).⁴⁵ We assess 11 ADIS-C domains including: separation anxiety, social phobia, specific phobia, panic disorder, generalised anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, dysthymia, major depressive disorder, conduct disorder and oppositional defiant disorder. Screening positive for two or more anxiety problems on a similar measure has been shown to 1) have high sensitivity (0.75) and a low false positive rate (0.33); and 2) be associated with a five-fold increase in seeking treatment for an anxiety disorder.⁴⁶ Thus, children screening positive for two or more anxiety problems on the ADIS-C or one mood

disorder are classified as having an internalising comorbidity. Children screening positive to oppositional defiant or conduct disorder are classified as having an externalising comorbidity.

All researchers administering the ADIS-C hold a minimum fourth year degree in psychology and receive training and supervision from experienced clinical psychologist (ES). As interviewers are unblind to child sleep problem severity, approximately 10% of interviews are recorded (with verbal consent) to allow blinded cross-coding in order to calculate inter-rater reliability coefficients.

Table 1 summarises all other key outcome and exposure measures collected during the 12-month period. We also collect data on child demographics, medication use, as well as parent age and education level and neighborhood socioeconomic disadvantage score - measured by the census-based Socio-Economic Indexes for Areas Disadvantage Index for the child's postcode of residence (national mean 1000, SD 100; higher scores reflect greater advantage).⁴⁷

Sample size

The primary aim (1a) is to compare the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe and no/mild sleep problems. The established *Sleeping Sound with ADHD* RCT will provide data for 250 children with ADHD and moderate/severe sleep problems.⁴¹ Initial baseline data from the trial (n=64) demonstrated high ADIS-C completion rates (90%) and high proportions of co-occurring internalising and externalising comorbidities (42%). To detect a clinically meaningful difference of 15% in the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems (42%) and no/mild (27%) sleep problems, a further 150 children with no/mild sleep problems are required in the observational cohort study. Thus, our total study sample size is 400 children,

which provides 80% power at a 5% (2 sided) level of significance and allows for 10% of parents not completing the ADIS-C.

Data Analysis

Aims 1a and 1b involves analysis of baseline data only and thus will include the full sample of 400 children. For aims 2 and 3, which include longitudinal data analyses, we will exclude children in the intervention arm of the trial ($n \approx 125$) because of the expected effects of intervention on children's sleep. Thus the longitudinal sample includes ~ 125 children with moderate/severe sleep problems from the control arm and 150 children with no/mild sleep problems.

To address aim 1a, chi-squared tests will compare proportions of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems and those with no/mild sleep problems. Children will then be classified into four groups: 1) ADHD alone (reference group), 2) internalising comorbidity alone, 3) externalising comorbidity alone, and 4) both comorbidities (ie, internalising and externalising). Logistic regression will compare the odds of a moderate/severe sleep problem for children with each comorbidity type, to the reference group. The model will adjust for potential confounders identified *a priori* including child age, gender, family socio-demographic factors, use of stimulant medication, and ADHD symptom severity. Sensitivity analyses will be conducted excluding children who 1) are taking sleep medications, which could treat the sleep problem but not address comorbidities; 2) no longer meet criteria for an internalising comorbidity once sleep symptoms are excluded from the diagnostic criteria – to ensure that internalising comorbidities are not endorsed because of the child's sleep problems when they wouldn't be otherwise; and 3) including parent mental health (ie, total Depression Anxiety Stress Scale score) in the adjusted model to examine the influence of parent mental

health which could potentially be an outcome or a risk factor for comorbidities and sleep problem severity.

To address aim 1b, ie associations between comorbidities and sleep problem domains identified by the Child Sleep Habits Questionnaire,⁴² linear regression will estimate the mean change in domain scores for children with each type of comorbidity compared to ADHD alone (reference group). Both unadjusted and adjusted models controlling for confounders (outlined above for 1a) will be conducted.

To address aim 2, trajectories of sleep problems over the 12-month period, parent report of child sleep problems across the three time points (baseline, 6 and 12 month follow-up) will be characterised including timing and persistence of sleep problems. At each time point, sleep problems will be dichotomised as no/mild versus moderate/severe (for the purpose of this analysis, no/mild will be referred to as “no sleep problem” and moderate/severe as “a sleep problem”). It is anticipated that the categories derived will include the following groups: 1) never a problem; 2) no longer a problem at 12 months but has been previously; 3) problem at 12 months but not previously; and 4) persistent problem (ie, over all three time points). Using these categories as a nominal longitudinal outcome, multinomial logistic regression will examine baseline predictors (ie, internalising and externalising comorbidities, ADHD symptom severity, ADHD and sleep medication use, family socio-demographic factors, age, gender, autism spectrum disorders and parent mental health).

To address aim 3, child and family well-being at 12-months will be examined in relation to the patterns of sleep problems experienced over the preceding 12-months. Child and family outcomes will include child quality of life; child emotional, behavioural and social problems; school attendance; parent mental health, family functioning, and work attendance. Linear and logistic regression models will be specified according to the outcome and each

sleep problem trajectory will be included as a nominal predictor variable. Depending on the outcome examined, we will adjust for child factors including age, gender, ADHD and sleep medication use and family factors including socio-demographic factors. For outcomes other than parent mental health, this will additionally be considered as a predictive factor in sensitivity analyses. Unadjusted and adjusted regression models will be interpreted to consider how sleep problem trajectories may affect child and parent outcomes following a causal logic framework.⁴⁸

DISSEMINATION

Our study will elucidate the relationship between sleep problems and internalising and externalising comorbidities, which is likely to lead to better clinical identification of sleep problems and associated comorbidities. It will provide the first longitudinal data on sleep problems that are generalisable to the wider population of children with ADHD. These data will inform knowledge about the trajectories, predictors and the impact of sleep problems in children with ADHD, which will be highly clinically relevant. Limitations of this study include lack of direct assessments of child sleep and exclusion of non-English speaking families. The study also has a number of important strengths, including the large and geographically diverse sample and strong, standardised measures. We plan to present our findings at conferences and publish in international peer-reviewed journals. We will also inform Australian paediatricians - the main care providers for children with ADHD - through the *Australian Paediatric Research Network*.³³

Competing interests:

The authors declare they have no competing interests.

Funding: All aspects of the RCT, including follow-up, are funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC; No. 607362). All aspects of the cohort study involving children with no/mild sleep problems are funded by Centre for Community Child Health at the Royal Children’s Hospital and the Murdoch Childrens Research Institute. Ms Lycett is funded by the Hugh Rogers fund and a Murdoch Childrens Research Institute Postgraduate Health Scholarship. Dr Sciberras and Dr Mensah's positions are funded by an NHMRC Population Health Capacity Building Grant (No. 436914) and NHMRC Early Career Fellowships in Population Health (No. 1037159 and No. 1037449). A/Prof. Hiscock's position is funded by an NHMRC Career Development Award (No. 607351). Murdoch Childrens Research Institute is supported by the Victorian Government’s Operational Infrastructure Support Program.

Figures

Figure 1 – Participant flow

Tables

Table 1 – Measures collected across time points

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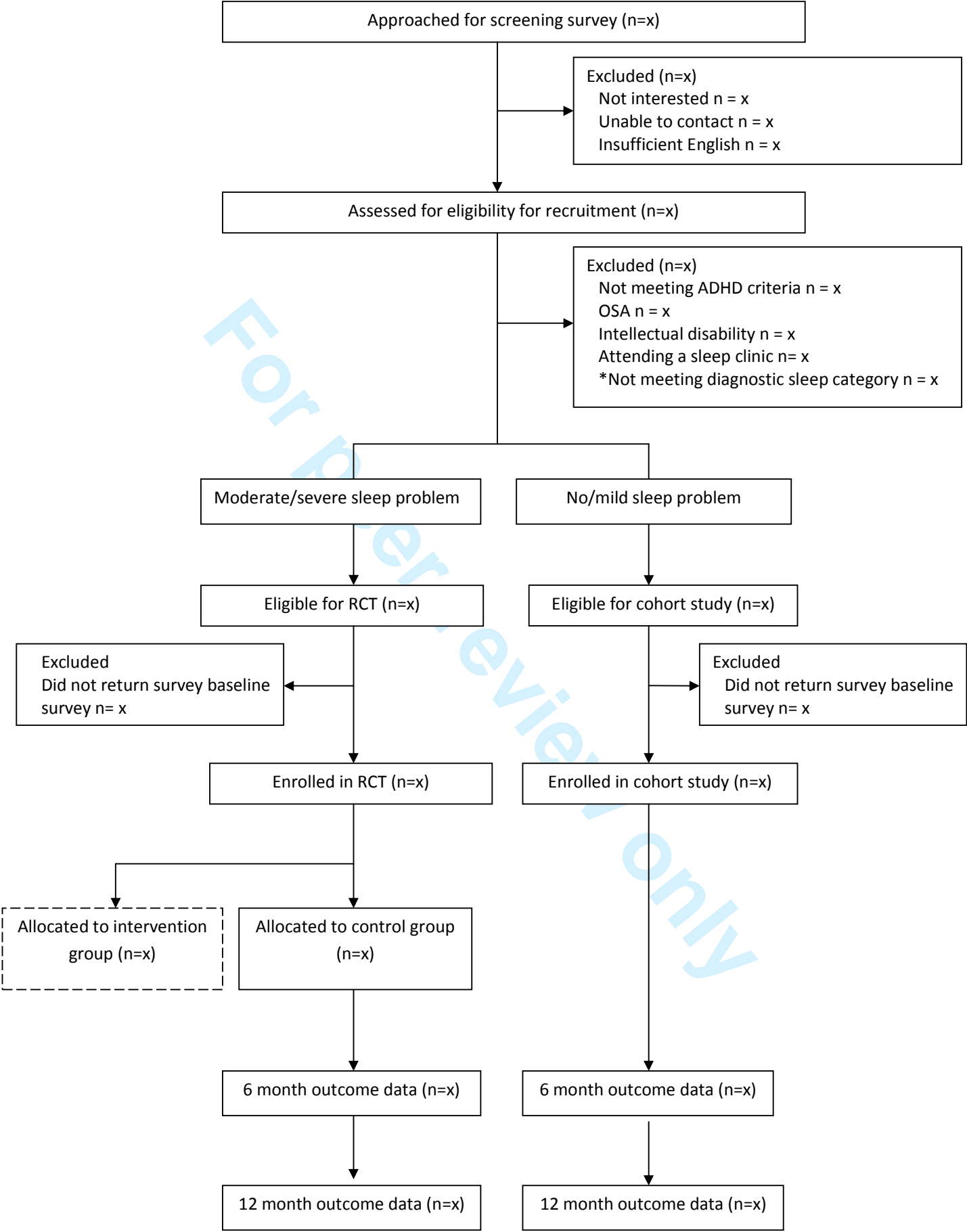
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Table 1. Measures collected across time points. ● Parent ▲ Teacher

Measures	Time Point			Additional information
	Baseline	6 mths	12 mths	
Child sleep/medication				
Children’s Sleep Habits Questionnaire ⁴²	●	●	●	A validated 33-item measure of disorders of initiating and maintaining sleep which can distinguish between samples of children attending a sleep clinical from community samples. It measures eight sleep problem domains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing and daytime sleepiness).
7-day sleep/medication log	●			Parents record their child’s bedtime at lights out, time asleep, night waking, morning wake time and medication use over a 7-day period during the school term.
Child behaviour and Quality of Life				
Daily Parent Rating of Evening/Morning Behaviour ⁴⁹	●	●	●	An 11-item rating of core ADHD symptoms and behavioural problems typically experienced over the past month.
ADHD IV Rating Scale (parent and teacher versions) ³⁶	● ▲	● ▲	● ▲	An 18-item validated scale measuring core symptoms i.e. inattention and impulsivity/hyperactivity.
Strengths and Difficulties Questionnaire ⁵⁰	● ▲	● ▲	● ▲	Assessment of behavioural and emotional problems. A validated 25-item measure designed for children 4 to 16 years. It provides scores on 5 subscales (hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems, and prosocial behaviour); a total problems score is derived from the first 4 subscales. Australian normative data are available for each subscale.
Pediatric Quality of Life Inventory – 4.0 ⁵¹	●	●	●	A validated 23-item measure for children aged 2 to 18 years. Provides total, physical, and psychosocial health summary scores, with higher scores indicating better health-related quality of life.
School attendance ⁶	●	●	●	School attendance measured over the preceding 3 months.
Parent/family outcomes				
Work attendance ⁶	●	●	●	Work attendance measured over the previous 3 months.
Depression Anxiety Stress Scale ⁵²	●	●	●	A validated 21-item measure of adult mental health with clinical cut points for each subscale: depression, anxiety and stress.
Child Health Questionnaire: Family Impact Scale ⁵³			●	Assessment of the emotional impact, time impact, and family activities subscales. Higher scores indicate better functioning. ⁵⁴



*These children had a moderate/severe sleep problem by parent report but it did not meet the *International Classification of Sleep Disorders* criteria for at least one behavioural sleep disorder⁴⁰ or correspond with night-time anxiety.



Behavioural sleep problems in children with attention deficit/hyperactivity disorder (ADHD): Protocol for a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004070.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Dec-2013
Complete List of Authors:	Lycett, kate; Murdoch Childrens Research Institute, Community Child Health Sciberras, Emma; Murdoch Childrens Research Institute, Community Child Health Mensah, Fiona; Murdoch Childrens Research Institute, Clinical Epidemiology and Biostatistics Unit Gulenc, Alisha; Murdoch Childrens Research Institute, Community Child Health Hiscock, Harriet; The Royal Children's Hospital, Centre for Community Child Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Mental health
Keywords:	Community child health < PAEDIATRICS, Child & adolescent psychiatry < PSYCHIATRY, SLEEP MEDICINE

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**Behavioural sleep problems in children with attention deficit/hyperactivity disorder (ADHD):
Protocol for a prospective cohort study.**

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Running title Behavioural sleep problems in children with ADHD

Date 18 September 2013

Word count 3161 (Abstract 298)

Key words attention deficit disorder with hyperactivity, sleep, child, comorbidity, mental
health

Abbreviations

ADHD Attention-deficit/hyperactivity disorder

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition

OSA Obstructive sleep apnoea

ADIS-C Anxiety Disorders Interview Schedule for Children/Parent version, fourth edition

RCT Randomised controlled trial

CSHQ Children’s Sleep Habits Questionnaire

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ABSTRACT

Background: Children with ADHD commonly experience behavioural sleep problems, yet these difficulties are not routinely assessed and managed in this group. Presenting with similar symptoms to ADHD itself, sleep problems are complex in children with ADHD and their aetiology is likely to be multifactorial. Common internalising and externalising comorbidities have been associated with sleep problems in children with ADHD; however, this relationship is yet to be fully elucidated. Furthermore, limited longitudinal data exist on sleep problems in children with ADHD, thus their persistence and impact remain unknown.

Study aims: In a diverse sample of children with ADHD, this study aims to: 1) quantify the relationship between sleep problems and internalising and externalising comorbidities; 2) examine sleep problem trajectories and risk factors; and 3) examine the longitudinal associations between sleep problems and child and family functioning over a 12-month period.

Methods and analysis: Prospective cohort study of 400 children with ADHD (150 with no/mild sleep problems, 250 with moderate/severe sleep problems) recruited from paediatric practices across Victoria, Australia. The children’s parents and teacher provide data at baseline and 6- and 12-months post enrolment. *Key measures:* parent-report of child’s sleep problem severity (no, mild, moderate, severe); specific sleep domain scores assessed using the Children’s Sleep Habits Questionnaire; internalising and externalising comorbidities assessed by the Anxiety Disorders Interview Schedule for Children IV/Parent version.

Analyses: Multiple variable logistic and linear regression models examining the associations between key measures, adjusted for confounders identified *a priori*.

Ethics and dissemination: Ethics approval has been granted. Findings will contribute to our understanding of behavioural sleep problems in children with ADHD. Clinically, they could improve the assessment and management of sleep problems in this group. We will seek to

publish in leading paediatric journals, present at conferences and inform Australian paediatricians through the *Australian Paediatric Research Network*.

For peer review only

ARTICLE SUMMARY

Article focus

- Behavioural sleep problems are common in children with ADHD as are internalising and externalising comorbidities; both of which are associated with poorer child and family well-being.
- However, the relationship between sleep problems and internalising and externalising comorbidities is yet to be quantified. Doing so may prompt clinicians to better address sleep problems, which do not appear to be routinely assessed and managed in the care of children with ADHD.
- Almost all studies investigating sleep problems in children with ADHD are cross-sectional and thus the trajectories of sleep problems and their relative impact on child and family well-being are unclear.

Key messages

- Elucidating the relationship between sleep problems and internalising and externalising comorbidities could inform their clinical assessment and management.
- This study will provide the first longitudinal data on the trajectories of sleep problems that are generalisable to the wider population of children with ADHD.
- This study will quantify the relative impact of sleep problems on child and family well-being over time, thereby informing clinicians and families of the relative importance of managing sleep problems in children with ADHD.

Strengths and limitations of the study

- The sample is recruited from a geographically diverse population of children with ADHD and represents the case mix seen in clinical practice, thus improving generalisability of the findings.
- Limitations of this study include lack of direct assessments of child sleep and exclusion of non-English speaking families.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder that leads to impairment across multiple domains including social and academic functioning.¹ ADHD affects up to 5% of children worldwide² and is commonly accompanied by sleep problems.³ Between 55-74% of parents report sleep problems in their child with ADHD⁴⁻⁸ and these are typically behavioural in nature (ie, extrinsic cause) and can include difficulty falling asleep, night waking and bedtime resistance.^{6,9} Primary sleep disorders (ie, intrinsic cause) such as restless leg syndrome and sleep disordered breathing are also elevated in children with ADHD compared to typically developing children.^{10,11,12} Yet, despite a long standing recognition of sleep problems prevalence,^{13,14} and evidence that they are associated with poorer child and family well-being,⁶ sleep problems do not appear to be routinely assessed or managed by clinicians caring for children with ADHD.⁶ Furthermore evidence based treatments for sleep disturbances in children with ADHD remain limited.¹⁵

Identifying sleep problems in children with ADHD is challenging. Sleep deprivation closely mimics symptoms attributed to ADHD (eg, inattention, hyperactivity)^{10,16} and objective and subjective measures of sleep often have disparate findings.^{4,16,17} Objective measures (eg, polysomnography, actigraphy) – the ‘gold standard’ – produce reliable findings for parameters such as sleep duration¹⁸ but feasibility and costs are often barriers to their use in large studies.¹⁹ In addition, they do not capture behavioural sleep problems such as bedtime resistance and limit setting disorders – which are more common in children with ADHD. On the other hand, subjective measures (eg, parent report) are a valid screening tool for behavioural sleep disorders¹⁸ yet may over-estimate sleep duration, under-estimate night-waking,^{18,19} and may also be influenced by parent mental health.²⁰ Parent report is, however, a valid measure for large studies where behavioural sleep problems are the key focus. Furthermore, parent report reflects parental concern, which is a key driver for seeking health professional advice around sleep.²¹

The mechanisms associated with sleep problems in children with ADHD are complex and appear multi-factorial.¹⁰ Both sleep problems and ADHD are regulated by the central nervous system, thus there is a strong neurobiological overlap^{3, 10, 22} and their relationship is likely bi-directional.^{10, 23} Empirically, this is supported by the recognition that ADHD symptom severity worsens in the presence of sleep problems.^{6, 24, 25} Similarly, stimulant medications (eg, methylphenidate), which also work on the central nervous system, have been associated with sleep problems, in particular delayed sleep-onset latency.^{13, 20-22} Yet, in some circumstances stimulants may improve sleep²⁶ and many stimulant naïve children also experience sleep problems⁵, therefore other factors have received increasing investigation.

In typically developing children, sleep problems have been associated with internalising (eg, mood disorders, anxiety disorders) and externalising (oppositional defiant disorder, conduct disorder) comorbidities.²⁷ Research suggests that this is also the case for children with ADHD.^{24, 25, 28-30} However, this relationship is yet to be fully elucidated. Previous studies are often limited to single clinical samples^{8, 24, 25, 31, 32} and exclude children with common comorbidities or those taking ADHD medication.^{28, 29, 33} Furthermore, researchers are yet to consider children with co-occurring internalising and externalising comorbidities. Elucidating the relationship between sleep problems and internalising and externalising comorbidities in children with ADHD is likely to inform clinical practice around the assessment and management of sleep problems in this group.

Clinical management of sleep problems is also restricted by the lack of longitudinal data, which would inform the prognosis and thus the relative importance of managing sleep problems in children with ADHD. Although behavioural sleep problems are common in typically developing children, they are often transient and likely to resolve naturally.³⁴ However, in children with major depression, sleep problems have been shown to persist even after successful treatment.³⁵ The nature and persistence of sleep problems in children with

ADHD is unclear. In a large population-based longitudinal study, Scott et al. showed that children with ADHD slept less than typically developing children from infancy to age 11 years, and this was statistically significant age 5.9, 6.9 and 9.7 years.²³ This study has made a substantial contribution to the literature, yet its focus is limited to sleep duration and does not consider other common sleep problems. In a longitudinal study of a clinical sample of children referred with ADHD, anxiety, or both (n=76, age 7 to 13 years), sleep problems were more likely to persist in this group over an 18-month period compared with a control group of children without a history of accessing mental health services recruited from nearby schools (n=31).³⁶ The generalisability of these findings is limited by the small sample size and mixed sample of children with anxiety alone and ADHD/anxiety. Longitudinal studies that can be generalised to the wider population of children with ADHD are required to understand trajectories and prognosis of sleep problems in ADHD.

Furthermore, longitudinal data could assess the burden of sleep problems in ADHD. Cross-sectionally, children with ADHD and parent-reported sleep problems have higher ADHD symptom severity,^{24, 25, 37} poorer quality of life, daily functioning and school attendance; and their caregivers are also more likely to be miss work and have poorer mental health⁶ compared to children with ADHD without sleep problems. However, the cross-sectional nature of these studies makes it impossible to delineate the sequence of sleep problems and other difficulties with functioning. Identifying the long-term impact sleep problems have on the functioning of children with ADHD is important to rationalise time and financial investment in the identification and management of sleep problems by health professionals and families.

STUDY AIMS

Through establishing a diverse cohort of children with ADHD recruited from multiple clinical practices, our study aims to address some of the previous limitations identified. The primary aim of the study is to examine associations between sleep problems and internalising and externalising comorbidities, considering parent reported moderate/severe behavioural sleep problems (Aim 1a); and sleep problem domains (eg, bedtime resistance, sleep anxiety) (Aim 1b). Through longitudinal study of the cohort over a one year period we will examine the trajectories of behavioural sleep problems and predictive risk factors (Aim 2); and examine longitudinal relationships between behavioural sleep problems and child and family well-being, specifically in the domains of child quality of life, school attendance, parent mental health, family functioning, and work attendance (Aim 3).

METHODS AND ANALYSIS

Our prospective cohort study of children with ADHD (see Figure 1) runs from April 2011 to July 2014, encompassing participant recruitment, baseline and follow-up data collection and data analysis. The study is approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (30033; 28017) and Victorian Department of Education and Early Childhood Development (000573; 001307).

Study procedure

Paediatric practice recruitment

Personalised emails are sent to paediatricians working in public and private practice inviting them to assist with participant recruitment. In Australia, many general paediatricians work in public and private practice and the most common condition they manage is ADHD.³⁸ We identified paediatricians through the *Australian Paediatric Research Network*³⁸ and our knowledge of paediatricians who treat children with ADHD in the state of Victoria.

Paediatricians pre-identify children with ADHD who they have seen within the past 12 months. An 'opt out' letter, signed by the paediatrician, is sent to the child's primary caregiver, asking them to return the letter to the paediatrician if they *do not* wish to be contacted about the study. If caregivers do not 'opt out' within a two-week period, paediatricians pass the family's contact details onto the research team. This method has previously resulted in good uptake rates.³⁹

Family recruitment

The research team telephone families to assess eligibility. Interested, eligible families are mailed a participant information statement, consent form and parent baseline questionnaire. Families are enrolled upon receipt of written informed consent and the baseline questionnaire. To determine the extent of participation bias, data collected will be compared with non-participants including child gender, child age, and socioeconomic status of the family's immediate neighbourhood.

Participants

Inclusion criteria

Eligible children are aged 5 to 13 years who have a previous ADHD diagnosis, are currently experiencing ADHD symptoms and whose care-giver can report on their sleep, as below.

ADHD: Children identified by their treating paediatrician will have a confirmed diagnosis of ADHD, which in accordance with national recommendations requires confirmation of cross-situational impairment at kindergarten or school as well as home.⁴⁰ ADHD symptoms must also be current and are therefore assessed during the recruitment call, using the validated 18-item ADHD Rating Scale (DSM-IV)⁴¹ and study-designed questions

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3 assessing ADHD diagnosis as per DSM-IV.⁴² The study designed questions include: (a)
4 symptom duration ('Did your child have these symptoms for six months or longer before
5 he/she was diagnosed with ADHD?'); (b) age of onset ('Did your child have these symptoms
6 before he/she turned seven?'), and (c) cross-situational impairment ('Are these symptoms
7 present at home, school or when out socially (eg, in the park, visiting friends?').
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14 *Sleep problem* is determined by parent report of their child's sleep; parents are asked
15 "Has your child's sleep been a problem for you over the past 4 weeks?" If the parent
16 responds 'yes', they are asked to rate the severity of the problem (mild/moderate/severe).^{6, 34,}
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⁴³ In typically developing children, of those whose parents report a moderate/severe sleep problem, 90% fall in the clinical range on the validated Children's Sleep Habits Questionnaire (CSHQ).⁴⁴ Furthermore, parent report of moderate/severe sleep problems is associated with poorer child learning by blinded teacher report³⁴ and poorer child and family well-being.⁶ During the recruitment call if parents report that their child has a moderate/severe sleep problem they are asked several questions to establish whether the sleep problem meets the *International Classification of Sleep Disorders* criteria for at least one behavioural sleep disorder⁴⁵ or corresponds with night-time anxiety. Children with a moderate/severe sleep problem that meets at least one of these criteria are eligible for the *Sleeping Sound with ADHD study*, a randomised controlled trial (RCT) investigating whether treating sleep problems in children with ADHD can reduce ADHD symptoms.⁴⁶ Children with no/mild sleep problems are eligible for the *Attention to Sleep study*, an observational cohort study.

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Exclusion criteria

Children are excluded at the recruitment call if parents report any of the following criteria:

- 1) receiving specialised help for their sleep from a psychologist or a specialised sleep clinic – an important consideration for determining the efficacy of the intervention in the RCT;
- 2) serious medical condition (eg, severe cerebral palsy) or an intellectual disability (IQ < 70);
- 3) suspected obstructive sleep apnoea (OSA). OSA is assessed using the three sleep disordered breathing items from the CSHQ.⁴⁷ Parents who report that their child ‘sometimes or usually snores loudly’, ‘stops breathing’ and/or ‘snorts/gasps’ during their sleep are contacted by a paediatrician (HH) for further assessment. If OSA is suspected, children are referred to appropriate services;
- 4) family does not speak sufficient English to complete recruitment call or questionnaires.

Data collection

Immediately post enrolment, families are sent a 7-day sleep and medication log to complete during a typical school week and scheduled for a phone interview to assess child internalising and externalising comorbidities (described below). If the primary caregiver consents, the child’s teacher is also sent a brief survey to assess classroom behaviour. Teachers are not informed of the child’s sleep problem severity or ADHD status. Follow-up surveys are sent to the child’s primary caregiver and teacher at 6- and 12-months post enrolment (see Table 1). Our follow-up period was limited to 12 months in order to harmonise with RCT data collection.

Measures

Internalising and externalising comorbidities are assessed by the Anxiety Disorders Interview Schedule for Children/Parent version IV (ADIS-C).⁴⁸ The ADIS-C is a semi-structured interview that allows, “for research purposes, reliable and valid diagnosis” according to DSM-IV criteria.”⁴⁹ The ADIS-C is validated for administration over the

telephone with parents - an important practical consideration - and yields excellent to acceptable 7-to-14-day test-retest reliability estimates for parents ($k=.65-1.00$).⁵⁰ We assess 11 ADIS-C domains including: separation anxiety, social phobia, specific phobia, panic disorder, generalised anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, dysthymia, major depressive disorder, conduct disorder and oppositional defiant disorder. Screening positive for two or more anxiety problems on a similar measure has been shown to 1) have high sensitivity (0.75) and a low false positive rate (0.33); and 2) be associated with a five-fold increase in seeking treatment for an anxiety disorder.⁵¹ Thus, children screening positive for two or more anxiety problems on the ADIS-C or one mood disorder are classified as having an internalising comorbidity. Children screening positive to oppositional defiant or conduct disorder are classified as having an externalising comorbidity.

All researchers administering the ADIS-C hold a minimum fourth year degree in psychology and receive training and supervision from experienced clinical psychologist (ES). As interviewers are unblind to child sleep problem severity, approximately 10% of interviews are recorded (with verbal consent) to allow blinded cross-coding in order to calculate inter-rater reliability coefficients.

Table 1 summarises all other key outcome and exposure measures collected during the 12-month period. We also collect data on child demographics, medication use, as well as parent age and education level, and neighborhood socioeconomic disadvantage score - measured by the census-based Socio-Economic Indexes for Areas Disadvantage Index for the child's postcode of residence (national mean 1000, SD 100; higher scores reflect greater advantage).⁵²

Sample size

The primary aim (1a) is to compare the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe and no/mild sleep problems. The established *Sleeping Sound with ADHD* RCT will provide data for 250 children with ADHD and moderate/severe sleep problems.⁴⁶ Initial baseline data from the trial (n=64) demonstrated high ADIS-C completion rates (90%) and high proportions of co-occurring internalising and externalising comorbidities (42%). To detect a clinically meaningful difference of 15% in the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems (42%) and no/mild (27%) sleep problems, a further 150 children with no/mild sleep problems are required in the observational cohort study. Thus, our total study sample size is 400 children, which provides 80% power at a 5% (2 sided) level of significance and allows for 10% of parents not completing the ADIS-C.

Data Analysis

Aims 1a and 1b involves analysis of baseline data only and thus will include the full sample of 400 children. For aims 2 and 3, which include longitudinal data analyses, we will exclude children in the intervention arm of the trial (n≈125) because of the expected effects of intervention on children's sleep. Thus the longitudinal sample includes ~ 125 children with moderate/severe sleep problems from the control arm and 150 children with no/mild sleep problems.

To address aim 1a, chi-squared tests will compare proportions of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems and those with no/mild sleep problems. Children will then be classified into four groups: 1) ADHD alone (reference group), 2) internalising comorbidity alone, 3) externalising comorbidity alone, and 4) both comorbidities (ie, internalising and

externalising). Logistic regression will compare the odds of a moderate/severe sleep problem for children with each comorbidity type, to the reference group. The model will adjust for potential confounders identified *a priori* including child age, gender, family socio-demographic factors, use of stimulant medication, and ADHD symptom severity. Sensitivity analyses will be conducted excluding children who 1) are taking sleep medications, which could treat the sleep problem but not address comorbidities; 2) no longer meet criteria for an internalising comorbidity once sleep symptoms are excluded from the diagnostic criteria – to ensure that internalising comorbidities are not endorsed because of the child’s sleep problems when they wouldn’t be otherwise; and 3) including parent mental health (ie, total Depression Anxiety Stress Scale score) in the adjusted model to examine the influence of parent mental health which could potentially be an outcome or a risk factor for comorbidities and sleep problem severity.

To address aim 1b, associations between comorbidities and sleep problem domains identified by the CSHQ,⁴⁷ linear regression will estimate the mean change in domain scores for children with each type of comorbidity compared to ADHD alone (reference group). Both unadjusted and adjusted models controlling for confounders (outlined above for 1a) will be conducted.

To address aim 2, trajectories of sleep problems over the 12-month period, parent report of child sleep problems across the three time points (baseline, 6 and 12 month follow-up) will be characterised including timing and persistence of sleep problems. At each time point, sleep problems will be dichotomised as no/mild versus moderate/severe (for the purpose of this analysis, no/mild will be referred to as “no sleep problem” and moderate/severe as “a sleep problem”). It is anticipated that the categories derived will include the following sleep problem groups: 1) never; 2) remitted (no longer a problem); 3) incident (developed problem over the 12 months); and 4) persistent (problem at all three time

points). Using these categories as a nominal longitudinal outcome, multinomial logistic regression will examine baseline risk factors (ie, internalising and externalising comorbidities, ADHD symptom severity, ADHD and sleep medication use, family socio-demographic factors, age, gender, autism spectrum disorders and parent mental health).

To address aim 3, child and family well-being at 12 months will be examined in relation to the patterns of sleep problems experienced over the preceding 12 months. Child and family outcomes will include parent reported child quality of life; parent and teacher reported child emotional, behavioural and social problems; and parent report of school attendance; parent mental health, family functioning, and work attendance. Linear and logistic regression models will be specified according to the outcome and each sleep problem trajectory will be included as a nominal predictor variable. Depending on the outcome examined, we will adjust for child factors including age, gender, ADHD and sleep medication use and family factors including socio-demographic factors. For outcomes other than parent mental health, this will additionally be considered as a confounding factor in sensitivity analyses. Unadjusted and adjusted regression models will be interpreted to consider how sleep problem trajectories may affect child and parent outcomes following a causal logic framework.⁵³

DISSEMINATION

Our study will elucidate the relationship between sleep problems and internalising and externalising comorbidities, which is likely to lead to better clinical identification of sleep problems and associated comorbidities. It will provide the first longitudinal data on sleep problems that are generalisable to the wider population of children with ADHD. These data will inform knowledge about the trajectories, risk factors and the impact of sleep problems in children with ADHD, which will be highly clinically relevant. If sleep problems are

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3 persistent for children with ADHD and associated with poorer outcomes longitudinally, then
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5 sleep interventions could provide a mechanism to improve outcomes for these children who
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7 already face considerable burden in our society. Limitations of this study include lack of
8
9 direct assessments of child sleep and exclusion of non-English speaking families. The study
10
11 also has a number of important strengths, including the large and geographically diverse
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13 sample and strong, standardised measures. We plan to present our findings at conferences and
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15 publish in international peer-reviewed journals. We will also inform Australian paediatricians
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17 - the main care providers for children with ADHD - through the *Australian Paediatric*
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19 *Research Network*.³⁸
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27 **Figures**

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30 Figure 1 – Participant flow
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33 **Tables**

34
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36 Table 1 – Measures collected across time points
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Author contribution

KL, HH, ES and FM conceived the study. KL coordinated the study and drafted the current manuscript, supervised by HH, ES and FM. AG participated in the coordination of the study and drafted the current manuscript, supervised by KL. All authors contributed, read and approved the final manuscript.

Funding: All aspects of the RCT, including follow-up, are funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC; No. 607362). All aspects of the cohort study involving children with no/mild sleep problems are funded by Centre for Community Child Health at the Royal Children's Hospital and the Murdoch Childrens Research Institute. Ms Lycett is funded by the Hugh Rogers fund and a Murdoch Childrens Research Institute Postgraduate Health Scholarship. Dr Sciberras and Dr Mensah's positions are funded by an NHMRC Population Health Capacity Building Grant (No. 436914) and NHMRC Early Career Fellowships in Population Health (No. 1037159 and No. 1037449). A/Prof. Hiscock's position is funded by an NHMRC Career Development Award (No. 607351). Murdoch Childrens Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they, their spouses, partners or children do not have any financial and non-financial relationships with companies that may be relevant to the submitted work to declare.

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Measures	Time Point			Additional information
	Baseline	6 mths	12 mths	
Child sleep/medication				
Children’s Sleep Habits Questionnaire ⁴⁷	●	●	●	A validated 33-item measure of disorders of initiating and maintaining sleep which can distinguish between samples of children attending a sleep clinical from community samples. It measures eight sleep problem domains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing and daytime sleepiness).
7-day sleep/medication log	●			Parents record their child’s bedtime at lights out, time asleep, night waking, morning wake time and medication use over a 7-day period during the school term.
Child behaviour and Quality of Life				
Daily Parent Rating of Evening/Morning Behaviour ⁵⁴	●	●	●	An 11-item rating of core ADHD symptoms and behavioural problems typically experienced over the past month.
ADHD IV Rating Scale (parent and teacher versions) ⁴¹	● ▲	● ▲	● ▲	An 18-item validated scale measuring core symptoms i.e. inattention and impulsivity/hyperactivity.
Strengths and Difficulties Questionnaire ⁵⁵	● ▲	● ▲	● ▲	Assessment of behavioural and emotional problems. A validated 25-item measure designed for children 4 to 16 years. It provides scores on 5 subscales (hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems, and prosocial behaviour); a total problems score is derived from the first 4 subscales. Australian normative data are available for each subscale.
Pediatric Quality of Life Inventory – 4.0 ⁵⁶	●	●	●	A validated 23-item measure for children aged 2 to 18 years. Provides total, physical, and psychosocial health summary scores, with higher scores indicating better health-related quality of life.
School attendance ⁶	●	●	●	School attendance measured over the preceding 3 months.
Parent/family outcomes				
Work attendance ⁶	●	●	●	Work attendance measured over the previous 3 months.
Depression Anxiety Stress Scale ⁵⁷	●	●	●	A validated 21-item measure of adult mental health with clinical cut points for each subscale: depression, anxiety and stress.
Child Health Questionnaire: Family Impact Scale ⁵⁸			●	Assessment of the emotional impact, time impact, and family activities subscales. Higher scores indicate better functioning. ⁵⁹

**Behavioural sleep problems in children with attention deficit/hyperactivity disorder (ADHD):
Protocol for a prospective cohort study.**

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Running title Behavioural sleep problems in children with ADHD

Date 18 September 2013

Word count ~~31612995~~ (Abstract 2948)

Key words attention deficit disorder with hyperactivity, sleep, child, comorbidity, mental health

Abbreviations

ADHD Attention-deficit/hyperactivity disorder

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition

OSA Obstructive sleep apnoea

ADIS-C Anxiety Disorders Interview Schedule for Children/Parent version, fourth edition

RCT Randomised controlled trial

CSHQ Children's Sleep Habits Questionnaire

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they, their spouses, partners or children do not have any financial and non-financial relationships with companies that may be relevant to the submitted work to declare.

Author contribution

KL, HH, ES and FM conceived the study. KL coordinated the study and drafted the current manuscript, supervised by HH, ES and FM. AG participated in the coordination of the study and drafted the current manuscript, supervised by KL. All authors contributed, read and approved the final manuscript.

ABSTRACT

Background: Children with ADHD commonly experience behavioural sleep problems, yet these difficulties are not routinely assessed and managed in this group. Presenting with similar symptoms to ADHD itself, sleep problems are complex in children with ADHD and their aetiology is likely to be multifactorial. Common internalising and externalising comorbidities have been associated with sleep problems in children with ADHD; however, this relationship is yet to be fully elucidated. Furthermore, limited longitudinal data exist on sleep problems in children with ADHD, thus their persistence and impact remain unknown.

Study aims: In a diverse sample of children with ADHD, this study aims to: 1) quantify the relationship between sleep problems and internalising and externalising comorbidities; 2) examine sleep problem trajectories ~~and predictors~~ risk factors; and 3) examine the ~~impact~~ longitudinal associations between of sleep problems ~~on and~~ children and ~~their~~ family ~~ies~~ well-being functioning over a 12-month period.

Methods and analysis: Prospective cohort study of 400 children with ADHD (150 with no/mild sleep problems, 250 with moderate/severe sleep problems) recruited from paediatric practices across Victoria, Australia. The children's parents and teacher provide data at baseline and 6- and 12-months post enrolment. *Key measures:* parent-report of child's sleep problem severity (no, mild, moderate, severe); specific sleep domain scores assessed using the Children's Sleep Habits Questionnaire; internalising and externalising comorbidities assessed by the Anxiety Disorders Interview Schedule for Children IV/Parent version.

Analyses: Multiple variable logistic and linear regression models examining the associations between key measures, adjusted for confounders identified *a priori*.

Ethics and dissemination: Ethics approval has been granted. Findings will contribute to our understanding of behavioural sleep problems in children with ADHD. Clinically, they could improve the assessment and management of sleep problems in this group. We will seek to

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publish in leading paediatric journals, present at conferences and inform Australian
paediatricians through the *Australian Paediatric Research Network*.

For peer review only

ARTICLE SUMMARY

Article focus

- Behavioural sleep problems are common in children with ADHD as are internalising and externalising comorbidities; both of which are associated with poorer child and family well-being.
- However, the relationship between sleep problems and internalising and externalising comorbidities is yet to be quantified. Doing so may prompt clinicians to better address sleep problems, which do not appear to be routinely assessed and managed in the care of children with ADHD.
- Almost all studies investigating sleep problems in children with ADHD are cross-sectional and thus the trajectories of sleep problems and their relative impact on child and family well-being are unclear.

Key messages

- Elucidating the relationship between sleep problems and internalising and externalising comorbidities could inform their clinical assessment and management.
- This study will provide the first longitudinal data on the trajectories of sleep problems that are generalisable to the wider population of children with ADHD.
- This study will quantify the relative impact of sleep problems on child and family well-being over time, thereby informing clinicians and families of the relative importance of managing sleep problems in children with ADHD.

Strengths and limitations of the study

- The sample is recruited from a geographically diverse population of children with ADHD and represents the case mix seen in clinical practice, thus improving generalisability of the findings.
- Limitations of this study include lack of direct assessments of child sleep and exclusion of non-English speaking families.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder that leads to impairment across multiple domains including social and academic functioning.¹ ADHD affects up to 5% of children worldwide² and is commonly accompanied by sleep problems.³ Between 55-74% of parents report sleep problems in their child with ADHD⁴⁻⁸ and these are typically behavioural in nature (ie, extrinsic cause) and can include difficulty falling asleep, night-time waking and bedtime resistance.^{6,9} Primary sleep disorders (ie, intrinsic cause) such as restless leg syndrome and sleep disordered breathing are also elevated in children with ADHD compared to typically developing children.^{10,11,12} Yet, despite a long standing recognition of sleep problems prevalence,^{13,14} and evidence that they are associated with poorer child and family well-being,⁶ sleep problems do not appear to be routinely assessed or managed by clinicians caring for children with ADHD.⁶ Furthermore evidence based treatments for sleep disturbances in children with ADHD remain limited.¹⁵

Identifying sleep problems in children with ADHD is challenging. Sleep deprivation closely mimics symptoms attributed to ADHD (eg, inattention, hyperactivity)^{10,16} and objective and subjective measures of sleep often ~~conclude have~~ disparate findings.^{4,16,17} Objective measures (eg, polysomnography, actigraphy) – the ‘gold standard’ – produce reliable findings for parameters such as sleep duration¹⁸ but feasibility and costs are often barriers to their use in large studies.¹⁹ In addition, they do not capture behavioural sleep problems such as bedtime resistance and limit setting disorders – which are more common in children with ADHD. On the other hand, subjective measures (eg, parent report) are a valid screening tool for behavioural sleep disorders¹⁸ yet ~~can may~~ over-estimate sleep duration, under-estimate night-waking,^{18,19} and ~~can may~~ also be influenced by parent mental health.²⁰ ~~Thus p~~Parent report is, however, a valid measure ~~ideal~~ for large studies where behavioural sleep problems are the key focus. Furthermore, parent report reflects parental concern, which is a key driver for seeking health professional advice around sleep.²¹

The mechanisms associated with sleep problems in children with ADHD are complex and appear multi-factorial.¹⁰ Both sleep problems and ADHD are regulated by the central nervous system, thus there is a strong neurobiological overlap^{3, 10, 22} and their relationship is likely bi-directional.^{10, 23} Empirically, this is supported by the recognition that ADHD symptom severity worsens in the presence of sleep problems.^{6, 24, 25} Similarly, stimulant medications (eg, methylphenidate), which also work on the central nervous system, have been associated with sleep problems, in particular delayed sleep-onset latency.^{13, 20-22} Yet, in some circumstances stimulants may improve sleep²⁶ and many stimulant naïve children also experience sleep problems⁵, therefore other factors have received increasing investigation.

In typically developing children, sleep problems have been associated with internalising (eg, mood disorders, anxiety disorders) and externalising (oppositional defiant disorder, conduct disorder) comorbidities.²⁷ Research suggests that this is also the case for children with ADHD.^{24, 25, 28-30} However, this relationship is yet to be fully elucidated. Previous studies are often limited to single clinical samples^{8, 24, 25, 31, 32} and exclude children with common comorbidities or those taking ADHD medication.^{28, 29, 33} Furthermore, researchers are yet to consider children with co-occurring internalising and externalising comorbidities. Elucidating the relationship between sleep problems and internalising and externalising comorbidities in children with ADHD is likely to inform clinical practice around the assessment and management of sleep problems in this group.

Clinical management of sleep problems is also restricted by the lack of longitudinal data, which would inform the prognosis and thus the relative importance of managing sleep problems in children with ADHD. Although behavioural sleep problems are common in typically developing children, they are often transient and likely to resolve naturally.³⁴ However, in children with major depression, sleep problems have been shown to persist even after successful treatment.³⁵ The nature and persistence of sleep problems in children with

ADHD is unclear. In a large population-based longitudinal study, Scott et al. showed that children with ADHD slept less than typically developing children from infancy to age 11 years, and this was statistically significant age 5.9, 6.9 and 9.7 years.²³ This study has made a substantial contribution to the literature, yet its focus is limited to sleep duration and does not consider other common sleep problems. In a longitudinal study of a clinical sample of children referred with -ADHD, anxiety, or both (n=76, age 7 to 13 years), sleep problems were more likely to persist in this group over an 18-month period compared with a control group of children without a history of accessing mental health services recruited from nearby schools (n=31).³⁶ The generalisability of these findings is limited by the small sample size and mixed sample of children with anxiety alone and ADHD/anxiety. Longitudinal studies that can be generalised to the wider population of children with ADHD are required to understand trajectories and prognosis of sleep problems in ADHD.

Furthermore, longitudinal data could assess the burden of sleep problems in ADHD. Cross-sectionally, children with ADHD and parent-reported sleep problems have higher ADHD symptom severity,^{24, 25, 37} poorer quality of life, daily functioning and school attendance; and their caregivers are also more likely to be miss work and have poorer mental health⁶ -compared to children with ADHD without sleep problems. However, the cross-sectional nature of these studies makes it impossible to delineate the sequence of sleep problems and other difficulties with functioning. Identifying the long-term impact sleep problems have on the functioning of children with ADHD is important to rationalise time and financial investment in the identification and management of sleep problems by health professionals and families.

STUDY AIMS

Through establishing a diverse cohort of children with ADHD recruited from multiple clinical practices, our study aims to address some of the previous limitations identified. The primary aim of the study is to examine associations between sleep problems and internalising and externalising comorbidities, considering parent reported moderate/severe behavioural sleep problems (Aim 1a); and sleep problem domains (eg, bedtime resistance, sleep anxiety) (Aim 1b). Through longitudinal study of the cohort over a one year period we will examine the trajectories of behavioural sleep problems and predictive risk factors (Aim 2); and examine longitudinal relationships between behavioural sleep problems and child and family well-being, specifically in the domains of child quality of life, school attendance, parent mental health, family functioning, and work attendance (Aim 3).

METHODS AND ANALYSIS

Our prospective cohort study of children with ADHD (see Figure 1) runs from April 2011 to July 2014, encompassing participant recruitment, baseline and follow-up data collection and data analysis. The study is approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (30033; 28017) and Victorian Department of Education and Early Childhood Development (000573; 001307).

Study procedure

Paediatric practice recruitment

Personalised emails are sent to paediatricians working in public and private practice inviting them to assist with participant recruitment. In Australia, many general paediatricians work in public and private practice and the most common condition they manage is ADHD.³⁸ We identified paediatricians through the *Australian Paediatric Research Network*³⁸ and our knowledge of paediatricians who treat children with ADHD in the state of Victoria.

Paediatricians pre-identify children with ADHD who they have seen within the past 12 months. An ‘opt out’ letter, signed by the paediatrician, is sent to the child’s primary caregiver, asking them to ~~contact the study~~ return the letter to the paediatrician team if they *do not* wish to be contacted about the study. If caregivers do not ‘opt out’ within a two-week period, paediatricians pass the family’s contact details onto the research team. This method has previously resulted in ~~a~~ good uptake rates.³⁹

Family recruitment

The research team telephone families to assess eligibility. Interested, eligible families are mailed a participant information statement, consent form and parent baseline questionnaire. Families are enrolled upon receipt of written informed consent and the baseline questionnaire. To determine the extent of participation bias, data collected will be compared with non-participants including child gender, child age, and socioeconomic status of the family's immediate neighbourhood.

Participants

Inclusion criteria

Eligible children are aged 5 to 13 years who have a previous ADHD diagnosis, are currently experiencing ADHD symptoms and whose care-giver can report on their sleep, as below.

ADHD: Children identified by their treating paediatrician will have a confirmed diagnosis of ADHD, which in accordance with national recommendations requires confirmation of cross-situational impairment at kindergarten or school as well as home.⁴⁰ ADHD symptoms must also be current and are therefore assessed during the recruitment call, using the validated 18-item ADHD Rating Scale (DSM-IV)⁴¹ and study-designed questions

assessing ADHD diagnosis as per DSM-IV.⁴² The study designed questions include: (a) symptom duration ('Did your child have these symptoms for six months or longer before he/she was diagnosed with ADHD?'); (b) age of onset ('Did your child have these symptoms before he/she turned seven?'), and (c) cross-situational impairment ('Are these symptoms present at home, school or when out socially (eg, in the park, visiting friends?').

Sleep problem is determined by parent report of their child's sleep; parents are asked "Has your child's sleep been a problem for you over the past 4 weeks?" If the parent responds 'yes', they are asked to rate the severity of the problem (mild/moderate/severe).^{6, 34, 43} In typically developing children, of those whose parents report a moderate/severe sleep problem, 90% fall in the clinical range on the validated Children's Sleep Habits Questionnaire (CSHQ).⁴⁴ Furthermore, parent report of moderate/severe sleep problems is associated with poorer child learning by blinded teacher report³⁴ and poorer child and family well-being.⁶ During the recruitment call if parents report that their child has a moderate/severe sleep problem they are asked several questions to establish whether the sleep problem meets the *International Classification of Sleep Disorders* criteria for at least one behavioural sleep disorder⁴⁵ or corresponds with night-time anxiety. Children with a moderate/severe sleep problem that meets at least one of these criteria are eligible for the *Sleeping Sound with ADHD study*, a randomised controlled trial (RCT) investigating whether treating sleep problems in children with ADHD can reduce ADHD symptoms.⁴⁶ Children with no/mild sleep problems are eligible for the *Attention to Sleep study*, an observational cohort study.

Exclusion criteria

Children are excluded at the recruitment call if parents report any of the following criteria:

- 1) receiving specialised help for their sleep from a psychologist or a specialised sleep clinic an important consideration for determining the efficacy of the intervention in the RCT;
- 2) serious medical condition (eg, severe cerebral palsy) or an intellectual disability (IQ < 70);
- 3) suspected obstructive sleep apnoea (OSA). OSA is assessed using the three sleep disordered breathing items from the CSHQ ~~Children's Sleep Habits Questionnaire~~.⁴⁷
Parents who report that their child 'sometimes or usually snores loudly', 'stops breathing' and/or 'snorts/gasps' during their sleep are contacted by a paediatrician (HH) for further assessment. If OSA is suspected, children are referred to appropriate services;
- 4) family does not speak sufficient English to complete recruitment call or questionnaires.

Data collection

Immediately post enrolment, families are sent a 7-day sleep and medication log to complete during a typical school week and scheduled for a phone interview to assess child internalising and externalising comorbidities (described below). If the primary caregiver consents, the child's teacher is also sent a brief survey to assess classroom behaviour. Teachers are not informed of the child's sleep problem severity or ADHD status. Follow-up surveys are sent to the child's primary caregiver and teacher at 6- and 12-months post enrolment (see Table 1). Our follow-up period was limited to 12 months in order to harmonise with RCT data collection.

Measures

Internalising and externalising comorbidities are assessed by the Anxiety Disorders Interview Schedule for Children/Parent version IV (ADIS-C).⁴⁸ The ADIS-C is a semi-structured interview that allows, "for research purposes, reliable and valid diagnosis" according to DSM-IV criteria."⁴⁹ The ADIS-C is validated for administration over the

telephone with parents - an important practical consideration - and yields excellent to acceptable 7-to-14-day test-retest reliability estimates for parents ($k=.65-1.00$).⁵⁰ We assess 11 ADIS-C domains including: separation anxiety, social phobia, specific phobia, panic disorder, generalised anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, dysthymia, major depressive disorder, conduct disorder and oppositional defiant disorder. Screening positive for two or more anxiety problems on a similar measure has been shown to 1) have high sensitivity (0.75) and a low false positive rate (0.33); and 2) be associated with a five-fold increase in seeking treatment for an anxiety disorder.⁵¹ Thus, children screening positive for two or more anxiety problems on the ADIS-C or one mood disorder are classified as having an internalising comorbidity. Children screening positive to oppositional defiant or conduct disorder are classified as having an externalising comorbidity.

All researchers administering the ADIS-C hold a minimum fourth year degree in psychology and receive training and supervision from experienced clinical psychologist (ES). As interviewers are unblind to child sleep problem severity, approximately 10% of interviews are recorded (with verbal consent) to allow blinded cross-coding in order to calculate inter-rater reliability coefficients.

Table 1 summarises all other key outcome and exposure measures collected during the 12-month period. We also collect data on child demographics, medication use, as well as parent age and education level, and neighborhood socioeconomic disadvantage score - measured by the census-based Socio-Economic Indexes for Areas Disadvantage Index for the child's postcode of residence (national mean 1000, SD 100; higher scores reflect greater advantage).⁵²

Sample size

The primary aim (1a) is to compare the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe and no/mild sleep problems. The established *Sleeping Sound with ADHD* RCT will provide data for 250 children with ADHD and moderate/severe sleep problems.⁴⁶ Initial baseline data from the trial (n=64) demonstrated high ADIS-C completion rates (90%) and high proportions of co-occurring internalising and externalising comorbidities (42%). To detect a clinically meaningful difference of 15% in the proportion of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems (42%) and no/mild (27%) sleep problems, a further 150 children with no/mild sleep problems are required in the observational cohort study. Thus, our total study sample size is 400 children, which provides 80% power at a 5% (2 sided) level of significance and allows for 10% of parents not completing the ADIS-C.

Data Analysis

Aims 1a and 1b involves analysis of baseline data only and thus will include the full sample of 400 children. For aims 2 and 3, which include longitudinal data analyses, we will exclude children in the intervention arm of the trial (n≈125) because of the expected effects of intervention on children’s sleep. Thus the longitudinal sample includes ~ 125 children with moderate/severe sleep problems from the control arm and 150 children with no/mild sleep problems.

To address aim 1a, chi-squared tests will compare proportions of co-occurring internalising and externalising comorbidities between children with moderate/severe sleep problems and those with no/mild sleep problems. Children will then be classified into four groups: 1) ADHD alone (reference group), 2) internalising comorbidity alone, 3) externalising comorbidity alone, and 4) both comorbidities (ie, internalising and

externalising). Logistic regression will compare the odds of a moderate/severe sleep problem for children with each comorbidity type, to the reference group. The model will adjust for potential confounders identified *a priori* including child age, gender, family socio-demographic factors, use of stimulant medication, and ADHD symptom severity. Sensitivity analyses will be conducted excluding children who 1) are taking sleep medications, which could treat the sleep problem but not address comorbidities; 2) no longer meet criteria for an internalising comorbidity once sleep symptoms are excluded from the diagnostic criteria – to ensure that internalising comorbidities are not endorsed because of the child's sleep problems when they wouldn't be otherwise; and 3) including parent mental health (ie, total Depression Anxiety Stress Scale score) in the adjusted model to examine the influence of parent mental health which could potentially be an outcome or a risk factor for comorbidities and sleep problem severity.

To address aim 1b, ie associations between comorbidities and sleep problem domains identified by the ~~Child Sleep Habits Questionnaire~~CSHQ,⁴⁷ linear regression will estimate the mean change in domain scores for children with each type of comorbidity compared to ADHD alone (reference group). Both unadjusted and adjusted models controlling for confounders (outlined above for 1a) will be conducted.

To address aim 2, trajectories of sleep problems over the 12-month period, parent report of child sleep problems across the three time points (baseline, 6 and 12 month follow-up) will be characterised including timing and persistence of sleep problems. At each time point, sleep problems will be dichotomised as no/mild versus moderate/severe (for the purpose of this analysis, no/mild will be referred to as “no sleep problem” and moderate/severe as “a sleep problem”). It is anticipated that the categories derived will include the following sleep problem groups: 1) never-a problem; 2) remitted (no longer a problem)~~-at 12 months but has been previously~~; 3) incident (developed problem over the at

12 months~~s~~ ~~but not previously~~; and 4) persistent ~~problem~~ (~~problem at ie, over~~ all three time points). Using these categories as a nominal longitudinal outcome, multinomial logistic regression will examine baseline ~~predictors~~ risk factors (ie, internalising and externalising comorbidities, ADHD symptom severity, ADHD and sleep medication use, family socio-demographic factors, age, gender, autism spectrum disorders and parent mental health).

To address aim 3, child and family well-being at 12~~_~~-months will be examined in relation to the patterns of sleep problems experienced over the preceding 12~~_~~-months. Child and family outcomes will include parent reported child quality of life; parent and teacher reported child emotional, behavioural and social problems; and parent report of school attendance; parent mental health, family functioning, and work attendance. Linear and logistic regression models will be specified according to the outcome and each sleep problem trajectory will be included as a nominal predictor variable. Depending on the outcome examined, we will adjust for child factors including age, gender, ADHD and sleep medication use and family factors including socio-demographic factors. For outcomes other than parent mental health, this will additionally be considered as a ~~predictive~~ confounding -factor in sensitivity analyses. Unadjusted and adjusted regression models will be interpreted to consider how sleep problem trajectories may affect child and parent outcomes following a causal logic framework.⁵³

DISSEMINATION

Our study will elucidate the relationship between sleep problems and internalising and externalising comorbidities, which is likely to lead to better clinical identification of sleep problems and associated comorbidities. It will provide the first longitudinal data on sleep problems that are generalisable to the wider population of children with ADHD. These data will inform knowledge about the trajectories, risk factors~~predictors~~ and the impact of sleep

problems in children with ADHD, which will be highly clinically relevant. If sleep problems are persistent for children with ADHD and associated with poorer outcomes longitudinally, then sleep interventions could provide a mechanism to improve outcomes for these children who already face considerable burden in our society. Limitations of this study include lack of direct assessments of child sleep and exclusion of non-English speaking families. The study also has a number of important strengths, including the large and geographically diverse sample and strong, standardised measures. We plan to present our findings at conferences and publish in international peer-reviewed journals. We will also inform Australian paediatricians - the main care providers for children with ADHD - through the *Australian Paediatric Research Network*.³⁸

Competing interests:

The authors declare they have no competing interests.

Funding: All aspects of the RCT, including follow-up, are funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC; No. 607362). All aspects of the cohort study involving children with no/mild sleep problems are funded by Centre for Community Child Health at the Royal Children's Hospital and the Murdoch Childrens Research Institute. Ms Lycett is funded by the Hugh Rogers fund and a Murdoch Childrens Research Institute Postgraduate Health Scholarship. Dr Sciberras and Dr Mensah's positions are funded by an NHMRC Population Health Capacity Building Grant (No. 436914) and NHMRC Early Career Fellowships in Population Health (No. 1037159 and No. 1037449). A/Prof. Hiscock's position is funded by an NHMRC Career Development Award (No. 607351). Murdoch Childrens Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program.

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Figures

Figure 1 – Participant flow

Tables

Table 1 – Measures collected across time points

For peer review only

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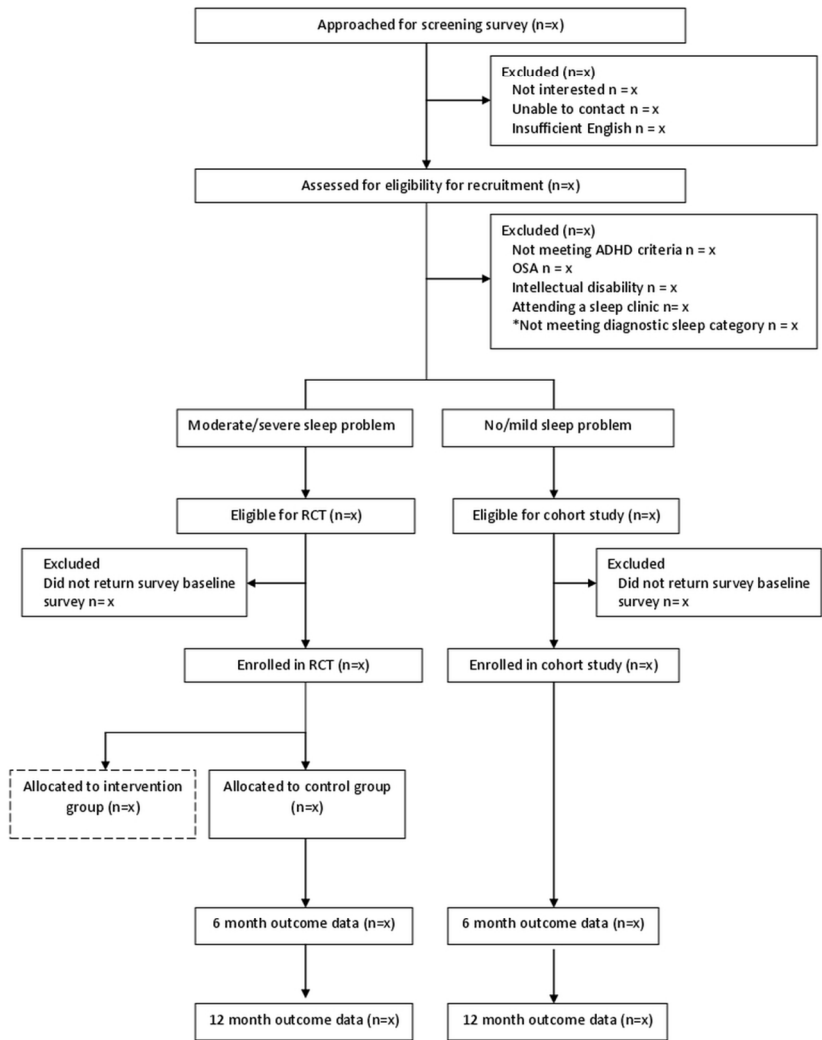
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Table 1. Measures collected across time points. ● Parent ▲ Teacher

Measures	Time Point			Additional information
	Baseline	6 mths	12 mths	
Child sleep/medication				
Children’s Sleep Habits Questionnaire ⁴⁷	●	●	●	A validated 33-item measure of disorders of initiating and maintaining sleep which can distinguish between samples of children attending a sleep clinical from community samples. It measures eight sleep problem domains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing and daytime sleepiness).
7-day sleep/medication log	●			Parents record their child’s bedtime at lights out, time asleep, night waking, morning wake time and medication use over a 7-day period during the school term.
Child behaviour and Quality of Life				
Daily Parent Rating of Evening/Morning Behaviour ⁵⁴	●	●	●	An 11-item rating of core ADHD symptoms and behavioural problems typically experienced over the past month.
ADHD IV Rating Scale (parent and teacher versions) ⁴¹	● ▲	● ▲	● ▲	An 18-item validated scale measuring core symptoms i.e. inattention and impulsivity/hyperactivity.
Strengths and Difficulties Questionnaire ⁵⁵	● ▲	● ▲	● ▲	Assessment of behavioural and emotional problems. A validated 25-item measure designed for children 4 to 16 years. It provides scores on 5 subscales (hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems, and prosocial behaviour); a total problems score is derived from the first 4 subscales. Australian normative data are available for each subscale.
Pediatric Quality of Life Inventory – 4.0 ⁵⁶	●	●	●	A validated 23-item measure for children aged 2 to 18 years. Provides total, physical, and psychosocial health summary scores, with higher scores indicating better health-related quality of life.
School attendance ⁶	●	●	●	School attendance measured over the preceding 3 months.
Parent/family outcomes				
Work attendance ⁶	●	●	●	Work attendance measured over the previous 3 months.
Depression Anxiety Stress Scale ⁵⁷	●	●	●	A validated 21-item measure of adult mental health with clinical cut points for each subscale: depression, anxiety and stress.
Child Health Questionnaire: Family Impact Scale ⁵⁸			●	Assessment of the emotional impact, time impact, and family activities subscales. Higher scores indicate better functioning. ⁵⁹

Figure 1. Participant flow



*These children had a moderate/severe sleep problem by parent report but it did not meet the *International Classification of Sleep Disorders* criteria for at least one behavioural sleep disorder⁴⁹ or correspond with night-time anxiety.

90x127mm (300 x 300 DPI)